PAPERS AND SHORT REPORTS

Effect of vaccination on severity and dissemination of whooping cough

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Abstract

A study was undertaken in general practice to clarify those factors, especially vaccination, that influence the clinical picture and infectivity of whooping cough in the community. Although the range of the disease encountered was fairly mild, its duration was notable (mean±SD 50·9±32·1 days). By using multiway contingency table analysis it was found that in the more severe cases of whooping cough vaccination significantly shortened the illness ($p<0.005$) and reduced the number of coughing spasms ($p<0.025$). The protective effect of the vaccine was most notable in modifying infectivity within the family: 19% of vaccinated family contacts of index patients in whom the disease had been confirmed bacteriologically developed the disease when exposed to it compared with 72% of non-vaccinated contacts ($p<0.001$).

These results show that whooping cough vaccination modifies the clinical illness and offers a worthwhile degree of protection to children exposed to the disease.

Introduction

The changing natural history of whooping cough as it occurs within the community is imperfectly understood, while the effectiveness of vaccination programmes to protect children exposed to this disease still engenders discord and debate.[1 2] A previous report[3] discussed the severity of an outbreak of whooping cough based on notified cases. To produce a more complete picture of the severity and spread of the disease and the effect of vaccination, however, we undertook a population study during the recent epidemic of whooping cough in the South-west Thames Region. We thought it important that the clinical diagnosis of whooping cough, especially in the milder cases, should be supported by bacteriological confirmation whenever possible, as otherwise any data produced would be open to various interpretations.

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Patients and methods

In June 1978 the morbidity pattern obtained from the recording practices of the Royal College of General Practitioners indicated that the incidence of whooping cough was increasing rapidly and a major epidemic was probable. This early warning allowed us to design a population study to evaluate the effect of vaccination on the severity and spread of the disease. A network of 68 interested general practitioners was recruited in the South-west Thames Region; these doctors had 136 200 patients under their care. The Public Health Laboratories at Tooting, Guildford, and Epsom undertook the bacteriological investigations required.

Patient selection—When a suspected case of whooping cough was seen in one of the practices a specially trained nurse attached to the practice was notified and per nasal swabs were taken from the suspected case and whenever possible from the siblings and parents. For the purpose of this study clinical whooping cough was suspected in an otherwise healthy child with a respiratory illness of more than eight days' duration characterised by spasmodic cough associated often with vomiting and sometimes with whooping. Medical and nursing surveillance was maintained until there was no further evidence of clinical respiratory disease in the family. A record card was completed daily by the parents indicating chemotherapy and the progressive nature of the disease.

Bacteriology—Per nasal swabs were placed in charcoal agar stabs and taken to the co-operating laboratories twice daily. Incubation was undertaken using blood-charcoal agar (Oxoid cm 119) with added cephalexin 40 mg/l in an atmosphere of 8% CO_2 for five days. Purification of isolated organisms required further incubation using blood-charcoal agar. Suspected organisms were confirmed by specific antisera and isolates sent to the Public Health Laboratory at Manchester for typing.

Diagnostic categories—Patients were placed in one of two categories with regard to the certainty of the diagnosis of whooping cough. The first category, group A, comprised patients from whom *Bordetella* *pertussis* had been isolated during the course of their illness; while the second category, group B, comprised patients with clinical whooping cough who had been in direct contact—that is, in the same family, class, or playgroup—as patients in group A but from whom it had not been possible to isolate *B pertussis*.

Clinical severity was measured by three variables. (1) The duration of the illness, which was taken from the onset of the disease and was the time interval, in days, until the child was completely recovered. (2) The severity of the cough, which was measured by recording the maximum number of coughing spasms per 24 hours experienced by the child at the peak of his illness. (3) The incidences of complications and admission to hospital. Complications were classified as major or minor, minor being defined as conjunctival haemorrhage or ulceration of the frenum, and major as apnoea with or without cyanosis, bronchitis, pneumonia, severe dehydration, convulsions, or admission to hospital.

Statistical analysis—Several factors such as age and vaccination state were found to be closely related. To study the effects of these factors on the severity of the disease a multiway contingency table analysis was undertaken[4 5]; using this method the significance of each of the explanatory factors could be measured. A greater proportion of vaccinated than non-vaccinated patients were untreated. To avoid any bias that this may have caused patients treated with erythromycin and those not given any antibiotics were analysed separately, as were index and contact cases.

Results

Group A comprised 218 patients and group B 440, and the analysis that follows is based on these 658 children and their contacts. In all, 1808 children were swabbed, but when there was an element of doubt about the diagnosis they were not included in the analysis.

CLINICAL PICTURE

It became apparent early in the study that the classical picture of whooping cough as typified by a moderately ill child with paroxysmal cough and characteristic whoop was not often encountered, though a persistent cough with vomiting was common. A striking clinical feature was the duration of the illness (mean 50·9 days). Compared with previous studies[3] there were relatively few major complications. Two children developed convulsions, one of whom had a history of febrile convulsions. Five children were admitted to hospital, one for social reasons. All five children recovered.

TREATMENT

Initial randomisation of patients suffering from whooping cough into a group treated with antibiotics and controls was not possible because the clinical management of each patient was the responsibility of the attending general practitioner. Consequently no direct comparison could be made between patients treated with antibiotics and the non-treated group. In practice, however, as might be expected, the treated patients were clinically the more severely ill children (table I).

EFFECT OF VACCINATION

Three aspects were considered: (1) Clinical severity as measured by the duration of the illness, severity of the cough, and incidence of complications. (2) Infectivity—that is, the relation of the spread of whooping cough in the family unit to the vaccination state of contacts within that unit. (3) Incidence of bacterial isolation—that is, the incidence of isolation of *B pertussis* related to the duration of the illness and the vaccination state of the patient.

Table II summarises the overall data. The severity of whooping cough as measured by the duration or severity of cough was not dependent on age; as might be expected, however, the percentage of vaccinated children increased with age.

TABLE I—*Relation between treatment and severity of disease according to vaccination state*

Treatment	No of patients		Severity of illness: Mean duration of illness (days)		Severity of illness: Mean No of coughing spasms/24 hours		Mean (±SD) age (years)	
	Not vaccinated	Vaccinated	Not vaccinated	Vaccinated	Not vaccinated	Vaccinated	Not vaccinated	Vaccinated
Erythromycin	226	142	55·7	46·4	13·0	10·5	2·7 ± 3·2	5·5 ± 3·7
Other antibiotic	52	38	65·4	51·6	14·9	15·1	3·7 ± 8·8	5·8 ± 5·5
Untreated (no antibiotic given)	99	101	47·5	42·3	12·6	9·2	3·3 ± 3·5	6·0 ± 5·1

TABLE II—*Relation between severity of illness and vaccination state*

Severity of illness expressed as:	Vaccination state: Vaccinated	Not vaccinated
Mean ± SE duration (days)	45·6 ± 2·0	54·9 ± 1·6
Mean ± SE maximum No of coughing spasms/24 hours	10·7 ± 0·5	13·2 ± 0·5
No with complications:		
Minor	19	25
Major	20	52
No of admissions to hospital	0	5
Total No of cases	281	377

Clinical severity in index cases

A multiway contingency table analysis was used to measure and separate the significance of the effects of vaccination state, age, and social class on the severity of the disease. In the analysis explanatory factors are each at two levels: vaccinated and non-vaccinated, social classes 1-3 and 4-5, and age 0-5 years and 6-12 years. The response factor indicates the severity of whooping cough and is expressed in three ways—that is, the duration of illness, the maximum number of coughing spasms per 24 hours, and the incidence of complications.

From this analysis we found that in the 136 patients not given antibiotics the data for both duration of illness and number of coughing spasms could be fitted well by a model that did not include dependence on the three explanatory factors. In the 263 patients treated with erythromycin, however, a model that excluded association between the three explanatory factors and the duration of the illness fitted badly ($p < 0·01$). This was also true for the number of coughing spasms ($p < 0·01$) (values of p being derived from the original contingency table analysis), although complications could be so described ($p > 0·1$). Further fitting of models suggested that duration was associated with vaccination state but not with age or social class; and that the number of coughing spasms was associated with vaccination state and age but not with social class.

TABLE III—*Relation between vaccination state and severity of illness expressed as duration of illness and number of coughing spasms/24 hours (figures are numbers (%) of patients)*

Vaccination state	Duration of illness (days): 0–30	31–60	61+	No of coughing spasms/24 hours: 0–8	9–15	16+	Total No of patients
Not vaccinated	45 (20)	104 (46)	77 (34)	72 (32)	95 (42)	59 (26)	226
Vaccinated	64 (37)	64 (37)	45 (26)	83 (48)	62 (36)	28 (16)	173

TABLE IV—*Severity of whooping cough in index cases related to severity in contact cases, for each way of expressing severity (figures are numbers (%) of cases)*

Index case	Contact case			Total
	Duration (days)			
	0–30	31–60	61+	
Duration (days):				
0–30	14 (67)	6 (29)	1 (5)	21
31–60	27 (40)	33 (49)	7 (10)	67
61+	8 (13)	17 (28)	35 (58)	60 *
	No of coughing spasms/24 hours			
	0–8	9–15	16+	
No of coughing spasms/24 hours:				
0–8	32 (56)	19 (33)	6 (11)	57
9–15	15 (28)	29 (55)	9 (17)	53
16+	11 (29)	12 (32)	15 (39)	38 **
	Complications			
	Absent	Mild	Severe	
Complications:				
Absent	104 (87)	8 (7)	7 (6)	119
Mild	7 (64)	2 (18)	2 (18)	11
Severe	2 (11)	1 (6)	15 (83)	18 ***

*Pearson's correlation coefficient = 0·6488.
**Pearson's correlation coefficient = 0·5238.
***Cramer's V = 0·4912.

TABLE V—*Outcome in contacts of patients in group A (those in whom B pertussis was isolated) and in contacts of all index cases studied. Figures are numbers (%) of cases)*

Clinical outcome	Contacts of group A: Vaccination state: Not vaccinated	Partially vaccinated*	Fully vaccinated	Total	Contacts of all index cases: Vaccination state: Not vaccinated	Partially vaccinated*	Fully vaccinated	Total
Remained asymptomatic	15 (28)	5 (71)	42 (81)	62 (55)	83 (47)	18 (67)	166 (78)	267 (64)
Developed whooping cough	39 (72)	2 (29)	10 (19)	51 (45)	92 (53)	9 (33)	47 (22)	148 (36)
% of positive isolates from contacts	62	50	40	57	52	44	30	45

*One to two injections given.
Difference between those not vaccinated and those partially and fully vaccinated: $\chi^2 = 30·649$ ($p<0·001$) for contacts of group A and $\chi^2 = 37·707$ ($p<0·001$) for contacts of all index cases.

TABLE VI—*Incidence of isolation of B pertussis (number (%) of cases): relation between duration of illness and vaccination state*

	Duration of illness: ≤4 weeks: Bacteriologically positive	≤4 weeks: Bacteriologically negative	>4 weeks: Bacteriologically positive	>4 weeks: Bacteriologically negative	Total
Vaccinated	15 (15·5)	82	58 (31·5)	126	281
Not vaccinated	14 (20·0)	56	131 (42·7)	176	377
Total	167		491		658

Duration of illness ≤4 weeks: $\chi^2 = 0·583$, NS. Duration of illness >4 weeks: $\chi^2 = 6·04$, $p<0·05$.

Table III shows the clinical severity of the index cases related to the vaccination state.

Clinical severity in contact cases

A multiway contingency table analysis was also used to examine the influence of various factors on the severity of the disease in contact cases. The explanatory factors, vaccination state and age, were again expressed at two levels, and the severity of whooping cough in the index case was an additional explanatory factor. The response factor, indicating the severity of the disease in the contacts, was again expressed in three ways—that is, duration of illness, maximum number of coughing spasms per 24 hours, and incidence of complications. Some contacts were given erythromycin by their doctors as a prophylactic measure. The cases were therefore grouped accordingly.

Some association was seen between the severity of whooping cough in contacts in all three aspects (duration, coughing spasms, and complications) and the three explanatory factors ($p<0·001$ in each case except for coughing spasms ($p<0·01$)). Values of p were derived from the original multiway contingency table analysis.

In the 214 contacts who did not receive antibiotics both vaccination state and the severity of the illness in the index case appeared to be necessary to describe the duration of the illness. For coughing spasms vaccination state alone gave a good fit, but complications required index severity plus either vaccination state or age for a satisfactory description. In the 167 contacts who received erythromycin the simplest model that adequately described the data for all three variables (duration, coughing spasms, and complications) was one containing vaccination state and index severity but not age. Table IV shows the relation between the severity of disease in the index cases and in their contacts.

Infectivity within family

Table V gives details of the spread of the disease within the family unit, which we believe to be the best measure of the effect of vaccination.

Bacterial isolation

Table VI shows the incidence of isolation of *B pertussis* from vaccinated and non-vaccinated patients.

Discussion

From this study based on a population survey carried out in general practice it may be seen that whooping cough remains a fairly long disease (mean duration 50·9 days) and has an incidence of complications of 17·6% but an incidence of admission to hospital of only 0·75%. The population under study, however, came from the relatively affluent higher social classes with all the attendant benefits. Direct comparison of these data cannot be made with data in studies based on notified cases or hospital data, as these must represent a more severe range of the disease.[6]

Identification of the different factors influencing the severity of the disease proved complex, there being, among other things, an association between age and the non-vaccinated state. By using a computer-based multiway contingency table analysis, however, the influence of the different factors of vaccination state, age, social class, and treatment on the severity of the disease could be measured.

We found that for the more severely ill index cases there was a significant relation between the severity of the disease, as measured by its duration ($p < 0.005$) and the severity of the cough ($p < 0.25$), with the vaccination state of the child but not with age or social class. This relation showed that 37% of vaccinated children had a short illness (less than 31 days) compared with only 20% of non-vaccinated children. Similarly, a mild cough (0-8 coughing spasms per 24 hours) was experienced by 48% of the vaccinated group and 32% of the non-vaccinated group.

In the contact cases the severity of the illness was influenced not only by the vaccination state but also by the severity of the illness in the index case. We could not distinguish from the data whether this latter influence was due to a genetic predisposition toward the disease or to associated environmental or social influences.

It has been suggested that the most valuable test of the effectiveness of a vaccine is how well it protects those children exposed to the disease in their normal environment. In this study we found that whooping cough vaccination conferred a significant degree of protection to children exposed to the disease ($p < 0.001$). In practical terms this means that about two out of 10 vaccinated children, when exposed in the family to whooping cough, developed the disease compared with seven out of 10 non-vaccinated children with a similar exposure. We found that the incidence of bacterial isolation of *B pertussis* was higher among non-vaccinated children throughout their illness, which may indicate an increased infectivity in this group.

This study shows, therefore, that whooping cough vaccination modifies the clinical illness and offers a worthwhile degree of protection to children exposed to the disease.

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SHORT REPORTS

Effect of emepronium bromide on lower oesophageal sphincter

Medical treatment of detrusor hyperreflexia and instability is often based on the use of parasympatholytics,[1] among which is emepronium bromide (Cetiprin). Side effects of emepronium bromide on the alimentary tract have been reported—namely, localised oesophageal injury and sporadic reports of ulceration of the oral mucosa. Recently 15 cases of oesophagitis during treatment with emepronium bromide were reviewed by Collins *et al*,[2] who added one case of changes in the oesophageal mucosal potential difference, suggesting gastro-oesophageal reflux as the cause of ulcerative oesophagitis.

Our investigation was aimed at assessing the effect of emepronium bromide on lower oesophageal sphincter pressure after parenteral and oral administration by using oesophageal manometry with a rapid pull-through technique.

Patients, methods, and results

Eleven patients (nine women and two men) with urinary incontinence due to detrusor instability entered the study. The median age was 54 (range 32-72) years. Treatment with emepronium bromide was indicated in all patients, none of whom had symptoms of oesophageal dysfunction. All gave their informed consent.

Oesophageal pressures were recorded with an Esophagus Motility Probe model 31™ (Kulite Semiconductor Products Inc).[3] Respiratory movements were measured by impedance recording. Swallowing was recorded as the registration of impedance across the neck. Lower oesophageal sphincter pressure was recorded using a rapid pull-through technique.[4] The pressure was calculated as the average of peak values given by the three transducers from three pull-throughs in the supine position during apnoea at sustained maximal expiration. The patients were fasting.

The trial was open, each patient being used as his own control. After the lower oesophageal sphincter pressure had been noted initially 50 mg emepronium bromide was administered intramuscularly. The pressure was noted 15 minutes after the injection, and a blood sample was obtained for determination of the serum concentration of emepronium bromide by gas chromatography. Thereafter, the patients were started on emepronium bromide 200 mg four times daily by mouth. Lower oesophageal sphincter pressure and serum emepronium bromide concentration were recorded after four weeks of treatment.

Only nine patients completed the four weeks of oral medication, as two suffered heartburn and dysphagia. Intramuscular administration of 50 mg emepronium bromide caused a significant reduction in lower oesophageal sphincter pressure ($p < 0.01$). After four weeks of oral medication the pressure was not significantly different from the pretreatment values ($p > 0.1$) (table). Higher serum concentrations of emepronium bromide were found after intramuscular than oral treatment ($p < 0.01$).

Effect of emepronium bromide on lower oesophageal sphincter pressure and plasma drug concentrations. (Figures in parentheses are pressures after treatment expressed as percentages of pressures before treatment)

Case No	Lower oesophageal sphincter pressure (mm Hg)			Plasma emepronium bromide concentration (µg/l)	
	Before treatment	15 minutes after 50 mg intramuscularly	After 200 mg four times daily for four weeks	15 minutes after 50 mg intramuscularly	After four weeks' oral treatment
1	43	34 (79)	35 (81)	963	112
2	48	30 (63)	53 (110)	705	0
3	46	23 (50)	*	727	*
4	36	19 (53)	40 (111)	1272	12
5	42	15 (36)	31 (74)	765	50
6	27	19 (70)	24 (89)	1370	106
7	19	17 (89)	14 (74)	913	52
8	60	40 (67)	*	2153	*
9	23	18 (78)	25 (109)	1089	99
10	27	19 (70)	28 (104)	925	108
11	21	19 (90)	25 (119)	729	46
Median	36	19 (70)	28 (104)	925	52
	$p < 0.01$†			$p < 0.01$†	

*Patient stopped treatment because of dysphagia and heartburn.
†Significance assessed using Wilcoxon's test.

Comment

The peak serum concentration of emepronium occurs about 15 minutes after intramuscular administration of the drug, a dose of 50 mg being sufficient to elicit relaxation of the bladder.[5] The present